PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
ACH/63267/000		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/06641	24.06.2003	29.07.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K38/00		
Applicant		
THERAPICON SRL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.11.2003	19.10.2004
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06641

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-30 as originally filed

Claims, Numbers

1-24 received on 28.11.2003 with letter of 27.11.2003

Drawings, Sheets

1-23 filed with telefax on 11.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	22-23
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	22-23
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 22-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Documents

1.1. The present application refers to a the use of THAM to enhance the absorption of substances of peptide nature through the nasal mucus-lined epithelium.

1.2. Reference is made to the following documents:

D1: EP-A-0 726 075
D2: WO 01 52937 A
D3: IT-B-1 243 742
D4: EP-A-0 302 772

1.3. The document D4 was not cited in the international search report. A copy of the document is appended hereto.

1.4. Reference is made to the passages cited in the International Search Report.

1.5. The amendments filed with the International Bureau under Article 19(1) do **not** introduce subject-matter which extends beyond the content of the application as filed and are therefore allowable (Article 19(2) PCT).

2. Method of treatment

2.1. For the assessment of the present claims 22-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.2. However, it is noted that claims 22 and 23 do not refer to a specific disease but to a method of treating a patient in general.

3. Novelty

3.1. Document D1 discloses an endonasal composition containing calcitonin and tromethamine (synonyms: THAM; TRIS) in non inorganic saline solutions (comprising hydroxybenzoates and citric acid).

Although D1 does not provide any absorption data of calcitonin following to nasal administration, the compositions of the document are reported to be **'very suitable** for endonasal administration, when applied to the nasal mucosa' (see page 2, line 41-42).

3.2. D2 teaches a stable formulation of a monomeric insulin analog comprising a **mixed buffer system** comprising TRIS combined with a buffering molecule (e.g., citrate buffer).

Although D2 does not report any absorption figure of insulin or any other peptide, following the absorption of the solution into the nasal cavity, the formulation may be explicitly administered as an aerosol for absorption in the nasal cavity (page 16, line 19-20). Preferred parenteral routes for administering include nasal routes (page 16, line 8).

The formulations are administered to treat several diseases such as diabetes of hypoglycemia (page 16, line 23-24).

3.3. D3 refers to a nasal formulation comprising calcitonin, hydroxybenzoates, citric acid and monobasic tromethamine citrate. D3 discloses the use of tromethamine

citrate monobasic as buffering agent in order to provide exclusively a better **stability** of calcitonins.

3.4. None of the prior art documents discloses the specific **use of THAM as an absorbefacient agent** for the nasal absorption of several peptides. Claims 1-21 are therefore novel in terms of Art. 33(2) PCT.

3.5. However, a method for treating a patient with a formulation comprising THAM and an active peptide is already disclosed in prior art (see 4.1. and 4.2.). Thus, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 22 and 23 is not new in the sense of Article 33(2) PCT.

4. Inventive step

4.1. The present application refers to a the use of THAM to enhance the absorption of substances of peptide nature through the nasal mucus-lined epithelium.

4.2. Document D4, which is considered to represent the most relevant state of the art, discloses a nasal administration composition containing a physiologically active peptide as active ingredient can be efficiently absorbed through nasal mucosa by the addition of a water-soluble organic acid as an absorption promoter.

3.2. The subject-matter of claim 1 differs from document D4 in that THAM is used as absorption enhancer for peptides instead of water-soluble organic acids.

3.3. In the light of the present claims, description and having regard to the prior art, the problem to be solved by the above claims can be formulated as 'provision of further absorption enhancers for improved absorption of pharmaceutically active peptides through the nasal mucosa'.

3.4. The authors have unexpectedly found that tromethamine (THAM) which has been used as buffer and stabilizer can improve the absorption of therapeutic doses of active peptides through the nasal mucosa.

3.5. None of the presently available prior art documents discloses or points towards the use of THAM as penetration enhancer for proteins. Thus, nothing in the prior art would have motivated a skilled person to use THAM for the purpose claimed in

the present application (as an absorbefacient).

3.6. Therefore, claim 1 and dependent claims 2-21 are considered as inventive (Art. 33(3) PCT).

CLAIMS:

1. Use of THAM [tris(hydroxymethyl)aminomethane] in a pharmaceutical formulation as a selective absorbefacient to enhance the absorption of substances of peptide nature through the nasal mucus-lined-epithelium; wherein the pharmaceutical formulation comprises a therapeutically effective amount of active peptide, its pharmaceutically acceptable salt or its peptidic fragment; in a pharmaceutically acceptable, aqueous liquid diluent or carrier, said formulation being in a form suitable for nasal administration.

2. Use according to claim 1, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptide hormones or hormone derivatives, physiologically active lymphokines or monokines, peptidic enzymes, proteic vaccines, peptidic toxoids, personalised proteins derived from genoma, which can be conveniently used in a form suitable for nasal administration.

3. Use according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptide hormones or hormone derivatives such as buserelin, desmopressin, vasopressin, angiotensin, felypressin, octreotide, somatropin, thyrotropin (TSH), somatostatin, gosereline, thryptorelin and insulin (from caw and pig or synthetic or recombinant).

4. Use according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptide hormones or hormone derivatives such as protirelin, adrenocorticotropin (ACTH), prolactin, luteinizing hormone (LH), luteinizing hormone-release hormone (LH-RH), leuprorelin, calcitonin (human, chicken, eel, porcine or recombinant), carbocalcitonin and calcitonin gene related peptides (CGRP).

5. Use according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptide hormones or hormone derivatives such as kallikrein, parathyrin, glucagon, oxytocin, gastrin, secretin, leptin, nafarelin, serum gonadotropin, gonadotropin release factor, growth hormone, erytropoietin, hirudin, urograstrone, renin and human parathyroid hormone (h-PTH)

6. Use according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of physiologically active lymphokines or monokines such as interferon, interleukin, transferrin, histaglobulin, macrocortine, endorphins, enkephalins and neurotensin.

7. Use according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptidic enzymes such as lysozyme, urokinase and superoxide dismutase.

8. Use according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of proteic vaccines as acellular and cellular pertussis, diphtheria, tetanus and influenza vaccines.

9. Use according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptidic toxoids such as diphtheria, tetanus and from the group of personalised proteins derived from genoma.

10. Use according to any one of the preceding claims, wherein (1) the therapeutically effective amount of active nasal peptide, its pharmaceutically acceptable salt or its

peptidic fragment is in concentrations of 0.001 microgram/ml to 50.0 mg/ml or of 10 Units/ml to 20000 Units/ml, in relation to the therapeutically effective dose to be administered by endonasal route; and (2) THAM is in concentrations of 0.5 mg/ml to 30.0 mg/ml.

11. Use according to any one of the preceding claims, wherein (1) the therapeutically effective amount of active nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is in concentrations of 0.01 microgram/ml to 50.0 mg/ml or of 20 Units/ml to 12500 Units/ml; and (2) THAM is in concentrations of 2.0 mg/ml to 10.0 mg/ml.

12. Use according to any one of the preceding claims, wherein (1) the therapeutically effective amount of active nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is in concentrations of 0.05 microgram/ml to 10.0 mg/ml or of 100 Units/ml to 6000 Units/ml; and (2) THAM is in concentrations of 2.5 mg/ml to 4.5 mg/ml.

13. Use according to any one of the preceding claims, wherein said pharmaceutical formulation is in the form of ready-to-use or of reconstituted solution suitable for nasal administration in the form of a drop type or of a nasal spray.

14. Use according to any one of the preceding claims, suitably administrable in a metered single dose volume or in multiple doses thereof, said actuation comprising a metered dose volume between 50 microliters and 200 microliters.

15. Use according to any one of the preceding claims, wherein the aqueous liquid diluent or carrier comprises optionally other pharmaceutically acceptable auxiliary additives such as (a) hydrochloric or citric acid; (b) one or a mixture of methyl or/and propyl p-hydroxybenzoate; and (c) cysteine

16. Use according to claim 15, wherein the pharmaceutically acceptable, aqueous liquid diluent or carrier further comprises optionally other pharmaceutically acceptable auxiliary additives such as (a) hydrochloric acid 0.1 N in concentrations of 0.3 mg/ml to 50.0 mg/ml or citric acid in concentrations of 0.6 mg/ml to 60.0 mg/ml, more preferably of 2.8 mg/ml to 6.2 mg/ml; (b) one or a mixture of methyl or/and propyl p-hydroxybenzoate in concentrations not exceeding 0.3 mg/ml with a ratio of 2:1 to 20:1; and (c) cysteine in concentrations of 0.5 mg/ml to 10.0 mg/ml.

17. Use according to any one of claims 1 to 14, wherein said pharmaceutical formulation is in the form of a ready-to-use solution prepared by a method comprising the steps of: adding an adequate amount of distilled water to THAM, and optionally to methyl or/and propyl p-hydroxybenzoate, hydrochloric or citric acid and cysteine until complete dissolution; then dissolving at the end the adequate quantity of nasal peptide or its pharmaceutically acceptable salt or its peptidic fragment in said solution mixture.

18. Use according to claim 17, which method further includes the step of: filtering to make the solution suitable for nasal administration and filling a mono-disposable, or multidose device system with the filtrate, more preferably with progressive dose counting system.

19. Use according to any one of claims 1 to 14, wherein the pharmaceutical formulation is in the form of a reconstituted solution prepared by a method comprising:

preparing container n.° 1 with the nasal peptide either by dosing in the container the corresponding weight of powder of active nasal peptide or by preparing a suitable solution with a known concentration of the same, pouring the individually dosed volume into the container and then lyophilizing it to yield a lyophilized powder;

preparing container n.° 2 comprising the solvent mixture for reconstitution, resulting from adding an adequate amount of distilled water to THAM, and optionally to methyl or/and propyl p-hydroxybenzoate, hydrochloric or citric acid and cysteine until complete dissolution;

filtering to make the solution suitable for nasal administration; and

filling container n.° 2 with the filtrate.

20. Use according to claim 19, wherein container no .° 1 is prepared by dosing directly in the container the corresponding weight of powder 1e), or by preparing a suitable solution with a known concentration of the same, pouring the individually dosed volume directly into the container and then lyophilizing it directly in the container to yield a lyophilized powder.

21. Use according to claim 19 or 20, which further includes the step of: preparing the reconstituted solution at the time of starting its use by pouring the solvent mixture of container n.° 2 into container n.° 1; mixing thoroughly by rotation until complete dissolution; screwing the multidose device system on the neck of container n.° 1, comprising the reconstituted solution.

22. A method for treating a patient with a pharmaceutical formulating containing:

(1) THAM [tris (hydroxymethyl) aminomethane] as a selective absorption to enhance the absorption of substances of peptide nature through the nasal mucus-lined epithelium, and

(2) a therapeutically effective amount of active peptide, its pharmaceutically acceptable salt or its peptidic fragment

in a pharmaceutically acceptable aqueous liquid diluent or carrier, said formulation being in a form suitable for nasal administration, which method comprises intranasally

administering in the form of drop type or of nasal spray to said patient, a dosed volume of said formulation with the scope to elicit the desired pharmacological effect.

23. The method, according to claim 23, in which the administrable dose volume of the pharmaceutical formulation, comprised in a metered monodose disposable or in a multidose system thereof, is comprised between 50 microliters and 200 microliters per actuation.

AMENDED CLAIMS

[received by the International Bureau on 30 October 2003 (30.10.03);
original claim 1 replaced by new claim 1;
remaining claims unchanged]

1. A pharmaceutical formulation containing:
(1) THAM [tris(hydroxymethyl) aminomethane] as a selective absorbefacient to enhance through the nasal mucas-lined-epithelium the absorption of substances of peptide nature;
(2) a therapeutically effective amount of active nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment;
in a pharmaceutically acceptable, aqueous liquid diluent or carrier, said formulation being in a form suitable for nasal administration.

2. The pharmaceutical formulation, according to claim 1, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptide hormones or hormone derivatives, physiologically active lymphokines or monokines, peptidic enzymes, proteic vaccines, peptidic toxoids, personalised proteins derived from genoma, which can be conveniently used in a form suitable for nasal administration.

3. The pharmaceutical formulation, according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptide hormones or hormone derivatives such as buserelin, desmopressin, vasopressin, angiotensin, felypressin, octreotide, somatropin, thyrotropin (TSH), somatostatin, gosereline, thryptorelin and insulin (from caw and pig or synthetic or recombinant).

4. The pharmaceutical formulation, according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptide hormones or hormone derivatives such as protirelin, adrenocorticotropin (ACTH), prolactin, luteinizing hormone (LH), luteinizing hormone-release hormone (LH-RH),

leuprorelin, calcitonin (human, chicken, eel, porcine or recombinant), carbocalcitonin and calcitonin gene related peptides (CGRP).

5. The pharmaceutical formulation, according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptide hormones or hormone derivatives such as kallikrein, parathyrin, glucagon, oxytocin, gastrin, secretin, leptin, nafarelin, serum gonadotropin, gonadotropin release factor, growth hormone, erytropoietin, hirudin, urograstrone, renin and human parathyroid hormone (h-PTH)

6. The pharmaceutical formulation, according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of physiologically active lymphokines or monokines such as interferon, interleukin, transferrin, histaglobulin, macrocortine, endorphins, enkephalins and neurotensin.

7. The pharmaceutical formulation, according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptidic enzymes such as lysozyme, urokinase and superoxide dismutase.

8. The pharmaceutical formulation, according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of proteic vaccines as acellular and cellular pertussis, diphtheria, tetanus and influenza vaccines.

9. The pharmaceutical formulation, according to claim 1 or 2, wherein the nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is selected from the group of peptidic toxoids such as diphtheria, tetanus and from the group of personalised proteins derived from genoma.

10. The pharmaceutical formulation, according to any one of the preceding claims, wherein (1) the therapeutically effective amount of active nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is in concentrations of 0.001 microgram/ml to 50.0 mg/ml or of 10 Units/ml to 20000 Units/ml, in relation to the therapeutically effective dose to be administered by endonasal route; and (2) THAM is in concentrations of 0.5 mg/ml to 30.0 mg/ml.

11. The pharmaceutical formulation, according to any one of the preceding claims, wherein (1) the therapeutically effective amount of active nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is in concentrations of 0.01 microgram/ml to 50.0 mg/ml or of 20 Units/ml to 12500 Units/ml; and (2) THAM is in concentrations of 2.0 mg/ml to 10.0 mg/ml.

12. The pharmaceutical formulation, according to any one of the preceding claims, wherein (1) the therapeutically effective amount of active nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment is in concentrations of 0.05 microgram/ml to 10.0 mg/ml or of 100 Units/ml to 6000 Units/ml; and (2) THAM is in concentrations of 2.5 mg/ml to 4.5 mg/ml.

13. The pharmaceutical formulation, according to any one of the preceding claims, wherein said pharmaceutical formulation is in the form of ready-to-use or of reconstituted solution suitable for nasal administration in the form of a drop type or of a nasal spray.

14. The pharmaceutical formulation, according to any one of the preceding claims, suitably administrable in a metered single dose volume or in multiple doses thereof, said actuation comprising a metered dose volume between 50 microliters and 200 microliters.

15. A method for producing a pharmaceutical formulation according to any one of the preceding claims, wherein the aqueous liquid diluent or carrier comprises optionally other pharmaceutically acceptable auxiliary additives such as (a) hydrochloric or citric acid; (b) one or a mixture of methyl or/and propyl p-hydroxybenzoate; and (c) cysteine

16. The method according to claim 15, wherein the pharmaceutically acceptable, aqueous liquid diluent or carrier further comprises optionally other pharmaceutically acceptable auxiliary additives such as (a) hydrochloric acid 0.1 N in concentrations of 0.3 mg/ml to 50.0 mg/ml or citric acid in concentrations of 0.6 mg/ml to 60.0 mg/ml, more preferably of 2.8 mg/ml to 6.2 mg/ml; (b) one or a mixture of methyl or/and propyl p-hydroxybenzoate in concentrations not exceeding 0.3 mg/ml with a ratio of 2:1 to 20:1; and (c) cysteine in concentrations of 0.5 mg/ml to 10.0 mg/ml.

17. A method for producing a pharmaceutical formulation for nasal administration according to any one of claims 1 to 14, in the form of ready-to-use solution, said method comprising the steps of: adding an adequate amount of distilled water to THAM, and optionally to methyl or/and propyl p-hydroxybenzoate, hydrochloric or citric acid and cysteine until complete dissolution; then dissolving at the end the adequate quantity of nasal peptide or its pharmaceutically acceptable salt or its peptidic fragment in said solution mixture.

18. The method according to claim 17, which further includes the step of: filtering to make the solution suitable for nasal administration and filling a mono-disposable, or multidose device system with the filtrate, more preferably with progressive dose counting system.

19. A method for producing a pharmaceutical formulation for nasal administration, according to any one of claims 1 to 14, in the form of reconstituted solution, said method comprising:

preparing container n.° 1 with the nasal peptide either by dosing in the container the corresponding weight of powder of active nasal peptide or by preparing a suitable solution with a known concentration of the same, pouring the individually dosed volume into the container and then lyophilizing it to yield a lyophilized powder;

preparing container n.° 2 comprising the solvent mixture for reconstitution, resulting from adding an adequate amount of distilled water to THAM, and optionally to methyl or/and propyl p-hydroxybenzoate, hydrochloric or citric acid and cysteine until complete dissolution;

filtering to make the solution suitable for nasal administration; and

filling container n.° 2 with the filtrate.

20. The method according to claim 19, wherein container no .° 1 is prepared by dosing directly in the container the corresponding weight of powder 1e), or by preparing a suitable solution with a known concentration of the same, pouring the individually dosed volume directly into the container and then lyophilizing it directly in the container to yield a lyophilized powder.

21. The method according to claim 19 or 20, which further includes the step of: preparing the reconstituted solution at the time of starting its use by pouring the solvent mixture of container n.° 2 into container n.° 1; mixing thoroughly by rotation until complete dissolution; screwing the multidose device system on the neck of container n.° 1, comprising the reconstituted solution.

22. The pharmaceutical formulation, according to any one of claims 1 to 14, which have long shelf life, and when in-use, provide compositions of a therapeutically effective amount of

active nasal peptide, its pharmaceutically acceptable salt or its peptidic fragment.

23. A method for treating, with a pharmaceutical formulation according to any one of claims 1 to 14, a patient which comprises intranasally administering in the form of drop type or of nasal spray to said patient, a dosed volume of said formulation, comprising a therapeutically effective amount of nasal peptide or of its pharmaceutically acceptable salt or peptidic fragment conveniently combined with THAM in a pharmaceutically acceptable liquid, aqueous carrier or diluent, with the scope to elicit the desired pharmacological effect.

24. The method, according to claim 23, in which the administrable dose volume of the pharmaceutical formulation, comprised in a metered monodose disposable or in a multidose system thereof, is comprised between 50 microliters and 200 microliters per actuation.